(42 g, 1 mol) in 10 equal portions over a period of 24 h, another 10 ml of concentrated HCl being added after 20 h. The heterogeneous solution was cooled to 0 °C and filtered after standing for 6 h. The white solid was washed with cold water (25 ml), cold ethanol (25 ml), and anhydrous ether (100 ml), to afford analytically pure **11** (as the ⅓ hydrate)[9] (18.0 g, 89% yield): mp >300 °C; NMR [$(CD_3)_2SO$] δ 6.0–7.0 (br s, 1, NH), 7.0 (d of d, 1, 6-ArH, $J$ = 8, 2 Hz), 7.15 (d, 1, 8-ArH, $J$ = 2 Hz), 7.80 (d, 1, 5-ArH, $J$ = 8 Hz), 8.0–10.0 (br s, 2, $NH_2$); MS $m/e$ 195 ($M^+$ for $C_8H_6ClN_3O$).

Anal. Calcd for $C_8H_6ClN_3O \cdot \frac{1}{3}H_2O$: C, 47.65; H, 3.33; N, 20.84. Found: C, 47.93; H, 3.23; N, 20.75.

**2-Amino-7-chloro-6-nitro-4-quinazolone (13).** To a solution of 2-amino-7-chloro-4-quinazolone (1.0 g, 5.1 mmol) in concentrated $H_2SO_4$ (5 ml) at −10 °C (acetone–ice) was added 0.25 ml (1.2 equiv) of fuming $HNO_3$. The solution was heated on a steam bath for 10 min, then poured onto 200 ml of ice. The mixture was filtered to afford 1.0 g of **13** after drying at 100 °C in vacuo. On standing at 0 °C, 0.3 g of **13** as its $\frac{1}{2}H_2SO_4$ salt crystallized, analytically pure (96% total yield): mp >300 °C; NMR of free base [$(CD_3)_2SO$] δ 7.67 (s, 1, ArH), 8.2 (br s, 1, NH), 8.55 (s, 1, ArH), 10.1 (br s, 2, $NH_2$); MS $m/e$ 240 ($M^+$ for $C_8H_5ClN_4O_3$).

Anal. Calcd for $C_8H_5ClN_4O_3 \cdot \frac{1}{2}H_2SO_4$: C, 33.18; H, 2.09; N, 19.35. Found: C, 33.33; H, 2.10; N, 19.38.

**2-Amino-7-chloro-6,8-dinitro-4-quinazolone (12) and 13.** The above reaction was repeated using 0.5 ml (2.4 molar equiv) of fuming $HNO_3$. A yellow-red solid (1.4 g) was collected; hot filtration of the undissolved material from AcOH gave 0.38 g of **13**, identical with that isolated above (NMR and TLC, 20% ethanol, ½% AcOH in $CHCl_3$). Concentration and cooling of the AcOH gave analytically pure **12** (0.99 g, 68% yield): mp >300 °C; NMR [$(CD_3)_2SO$] δ 7.5 (br s, 2, $NH_2$), 8.62 (s, 1 ArH), 11.72 (s, 1, NH); MS $m/e$ 285 ($M^+$ for $C_8H_4ClN_5O_5$).

Anal. Calcd for $C_8H_4ClN_5O_5$: C, 33.64; H, 1.41; N, 24.52. Found: C, 33.68; H, 1.45; N, 24.26.

**2,7-Diamino-6-nitro-4-quinazolone (14).** A sealed tube containing 2-amino-7-chloro-6-nitro-4-quinazolone (0.42 g, 1.75 mmol) in ammonia-saturated butanol (20 ml at 0 °C) was heated at 180 °C for 24 h.[10] The solution was cooled to −20 °C, filtered, and washed with cold butanol (50 ml, −20 °C), triturated and washed with water (3 × 100 ml), and repurified from 90% AcOH, then from boiling 10% HCl, neutralized hot with concentrated $NH_4OH$, to afford **14** (0.330 g, 85% yield): mp >300°; NMR [$(CD_3)_2SO$] δ 6.55 (s, 1, ArH), 6.90 (br s, 2, $NH_2$), 7.42 (s, 2, $NH_2$), 8.0–9.5 (br s, 1, NH), 8.55 (s, 1, ArH); MS $m/e$ 221 ($M^+$ for $C_8H_7N_5O_3$).

An analytical sample was obtained by sublimation (240 °C, 0.01 mmHg) followed by recrystallization of the HCl salt from 20% HCl.

Anal. Calcd for $C_8H_8ClN_5O_3$: C, 37.29; H, 3.13; N, 27.18. Found: C, 37.42; H, 3.09; N, 26.85.

**6-Aminoimidazo[4,5-*g*]quinazol-8-one (1) from 14.** A solution of 2,7-diamino-6-nitro-4-quinazolone (0.10 g, 0.45 mmol) in formic acid (97%, 60 ml) was hydrogenated at 3 atm $H_2$ over 0.010 g of 10% Pd/C during 30 min. The catalyst was removed by filtration and the solution was heated at reflux for 2 h, after which the solvent was removed in vacuo. The pink residue was dissolved in 0.1 M HCl by heating, treated with decolorizing charcoal, and precipitated by addition of concentrated $NH_4OH$ followed by cooling. Preliminary purification could be achieved by stirring with ammonia-saturated ethanol at 25 °C. The white solid was removed by filtration and further purified by acid–base precipitation, yield 0.078 g (86%). The product was identical with that prepared from **9** by TLC, uv, and NMR.

**2,7-Diamino-6-nitro-4-quinazolone (14) from 5.** A solution of ethyl 2,4-diacetamido-5-nitrobenzoate (0.005 g) in absolute ethanol (5 ml) was saturated with HCl and heated at reflux for 20 min under nitrogen. Cyanamide was added to the solution and heating was continued for 36 h, at which time TLC (silica gel, EtOH–AcOH–$CHCl_3$) showed the formation of a compound identical with **14**.

**Acknowledgment.** This work was supported by Research Grant MPS 74-05911 from the National Science Foundation.

**Registry No.**—**1**, 60064-29-1; **1** 2HCl, 60064-30-4; **3**, 55204-24-5; **4**, 60064-31-5; **5**, 60064-32-6; **9**, 60064-33-7; **10**, 60064-34-8; **11**, 20198-18-9; **12**, 60064-35-9; **13**, 60064-36-0; **13** $\frac{1}{2}H_2SO_4$, 60064-37-1; **14**, 60064-38-2; **14** HCl, 60064-39-3; 4-nitroanthranilic acid, 619-17-0; 4-chloroanthranilic acid, 89-77-0.

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(7) The optimum ice–salt–water ratio (wt) was found to be 500:20:100 g.
(8) G. Heller and L. Hessel, *J. Prakt. Chem.*, **120**, 67 (1928).
(9) Drying over $P_2O_5$ in vacuo or at 140 °C in vacuo gave no decrease in the water content.
(10) More concentrated solutions of starting material in butanol are not advisable, as they tend to lead to the formation of many side products.

# Functionalization of a Steroidal C-18 Angular Methyl Group Using a 21,20-Chlorohydrin

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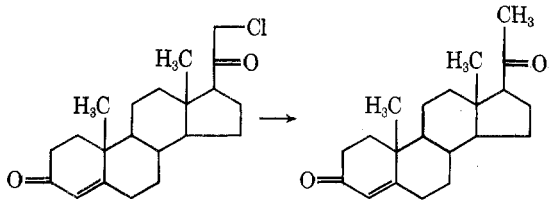
The preparation of a 3-keto-4-ene-21,20-chlorohydrin is described. Irradiation of its nitrite ester **7** furnished the C-18 nitroso compound **8**, which was converted into the oxime **10**. Selective acetylation of the oxime allowed oxidation of the C-20 alcohol to the chloro ketone **12**, and subsequent replacement of the C-21 chlorine by an acetoxy group to form **13**. All attempts at cleaving the oxime to generate the free 18-aldehyde failed. Elimination of acetic acid from the oxime acetate furnished 18-nitrilodeoxycorticosterone **15**. Oxidation of the oxime **10**, or the lead tetraacetate–iodine reaction on the chlorohydrin **5**, furnished the 21-chloro-18→20-lactone **16**, which was reduced to the 18,20β-diol **18**. Selective acetylation at C-18 allowed the oxidation of the C-20 alcohol to form 18-acetoxyprogesterone which was subsequently converted into 18-hydroxydeoxycorticosterone acetate.

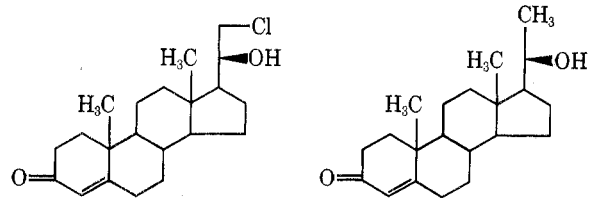
Ever since the elucidation of the structure of aldosterone as an 18-aldehyde, the functionalization of the angular methyl group at C-18 has posed a fascinating synthetic challenge. The most convenient synthesis of aldosterone was reported by Barton and involved the photolysis of corticosterone acetate 11β-nitrite to form aldosterone oxime.[1] At about the same time, Pappo described the synthesis of 18-hydroxyprogesterone (**1**) and 18-hydroxydeoxycorticosterone (**2**) from con-

essine,[2] while Wettstein et al. prepared 18-hydroxyprogesterone using the lead tetraacetate–iodine reaction.[3] The implication of 18-hydroxydeoxycorticosterone (**2**) as a hypertensive agent has recently resulted in increased interest in this area.[4] Kirk has published an elegant synthesis of **2** proceeding from **1**.[5] Barton has also recently described an improved synthesis of aldosterone,[6] while Kirk[7] has published a synthesis of 18-hydroxycorticosterone. At the same time Kalvoda has synthesized 18-oxodeoxycorticosterone, the oxidation product of **2** and the 11-deoxy analogue of aldosterone.[8,9] As a result, we would like to present our results on the functionalization of C-18 using a 21,20-chlorohydrin.

Proceeding from deoxycorticosterone, treatment with benzenesulfonyl chloride in collidine gave 21-chloroprogesterone (**3**). Subsequent reduction with lithium aluminum hydride gave a mixture of products, which, after oxidation of the allylic alcohol with dichlorodicyanobenzoquinone,[10] were separable by column chromatography. The first compound isolated was a relatively small amount of progesterone **4**.



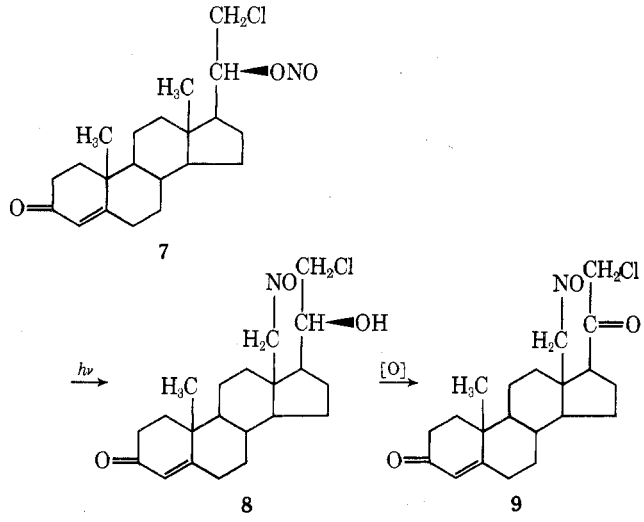
**3** **4**



**5** **6**

Presumably this was formed by 1,4 addition to the chloro ketone, forming the enolate. The inertness of steroidal enolates to $LiAlH_4$ reduction has recently been described.[14] The major compound isolated was 21-chloro-20$\beta$-hydroxypregn-4-en-3-one (**5**).[15] The structure of the compound was assigned by the enone absorptions in the uv and ir, its elemental analysis, and the NMR spectrum which showed the three C-20,21 protons as a multiplet centered at $\delta$ 3.58. The stereochemistry of the C-20 hydroxy group was initially assigned by analogy to the known reduction of 20-ketones,[16] but was later proved chemically (vide infra). The last compound isolated was 20$\beta$-hydroxypregn-4-en-3-one (**6**) and was identified by comparison with an authentic sample.[17] This compound was probably formed by hydrogenolysis of the chlorine–carbon bond in the chlorohydrin **5**. This halogen hydrogenolysis is known to be particularly facile.[18] The ratio of **4**:**5**:**6** is 16:55:29.

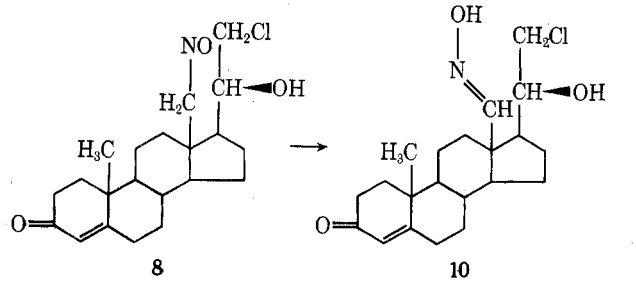
Reaction of chlorohydrin **5** with nitrosyl chloride in pyridine gave the 20$\beta$-nitrite ester **7**. Since **7** was rather unstable, it was prepared, kept cold, and used immediately. Irradiation of the nitrite ester **7** in benzene, under standard Barton reaction conditions,[19] gave the C-18 nitroso compound **8**, as its benzene solvate, routinely in 60% yield. This compound was identified as the nitroso compound rather than the isomeric oxime on the basis of its spectral data and further chemical reactions.[20] The uv spectrum of **8** showed the typical nitroso absorption at 300 nm,[21] while the geminal C-18 hydrogens appeared as doublets at $\delta$ 5.39 and 3.70 ($J$ = 15 Hz). The C-20,21 hydrogens appeared as a three-proton multiplet centered at $\delta$ 3.96. The isolation of the C-18 nitroso dimer **8** is apparently unique, since the oxime has usually been isolated. We found that it was possible to selectively oxidize the C-20 alcohol to the ketone



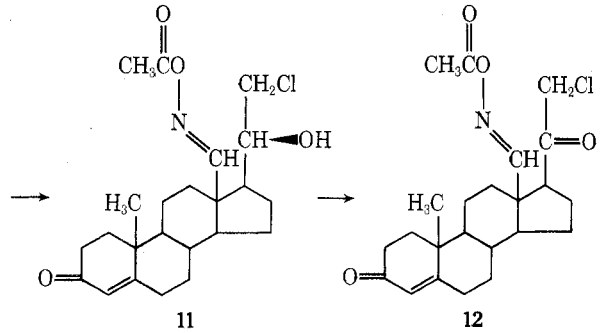
**7** **8** **9**

**9** in 92% yield without affecting the nitroso dimer linkage by using an excess of Jones reagent.[22] The continued presence of the nitroso group was indicated by its uv absorbtion at 298 nm and the presence of the C-18 hydrogens as doublets at $\delta$ 4.70 and 3.77 ($J$ = 14 Hz). The presence of the C-20 ketone was shown by an ir absorption at 1730 $cm^{-1}$. Unfortunately, all attempts to replace the C-21 chlorine in **9** by an acetoxy group failed; either starting material was recovered or highly polar material formed and the C-20 ketone absorption disappeared. This polar material was not further investigated, but nitrones are known to be formed from ketones and nitroso monomers.[1a]

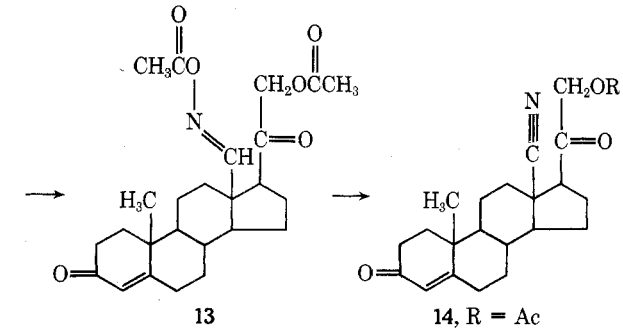
The nitrosochlorohydrin **8** could be converted into the oxime **10** in quantitative yield by refluxing in 2-propanol, or,



**8** **10**



**11** **12**

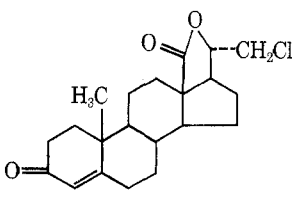


**13**

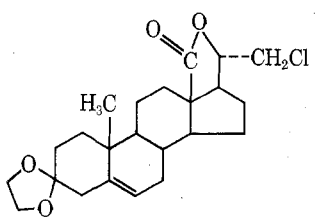
**14**, R = Ac
**15**, R = H

alternatively, simply by allowing **8** to stand in pyridine for a short time. The rearrangement of **8** to **10** in pyridine was a function of both the solvent and the C-20 alcohol since the C-20 ketone **9** did not rearrange. The conversion to oxime **10** was characterized by the disappearance of the nitroso uv absorption and the appearance of the oxime hydrogen as a singlet at $\delta$ 7.46. The resonances attributed to the C-18 hydrogens in **8** had also disappeared. Selective acetylation of the oxime **10** was accomplished in 69% yield by brief treatment with acetic anhydride in methylene chloride.[23] The oxime acetate was then converted to the chloro ketone **12**, in 79% yield, using Jones reagent, and subsequent brief refluxing with potassium iodide and potassium acetate in acetone furnished 18-acetoxyiminodeoxycorticosterone acetate (**13**) in 65% yield. All attempts to remove the oxime acetate group in **13** to form 18-oxodeoxycorticosterone acetate failed.[24,25] Either starting material was recovered, or elimination of acetic acid to form 18-nitrilodeoxycorticosterone acetate (**14**) occurred. On a preparative scale, **14** was prepared from **13** by refluxing in pyridine, and could be isolated in an overall yield of 25% starting from **8**. Since the saponification of **14** did not lead to a clean reaction, the acetate was removed by transesterification in methanol to yield 18-nitrilodeoxycorticosterone (**15**) in 69% yield.

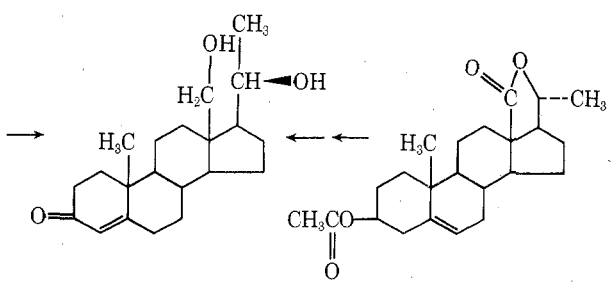
The 18-oxime chlorohydrin **10** was oxidized with Jones reagent to yield the 18→20 lactone **16** in 61% yield.[1c] The same lactone was available in 25% yield from the chlorohydrin **5** by means of the lead tetraacetate–iodine reaction.[26] The ketal **17** was prepared by vacuum distillation of an ethylene glycol solution of **16**,[27] in order to selectively reduce the lactone.



**16**



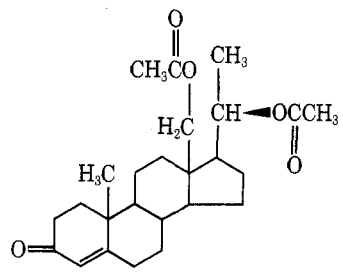
**17**



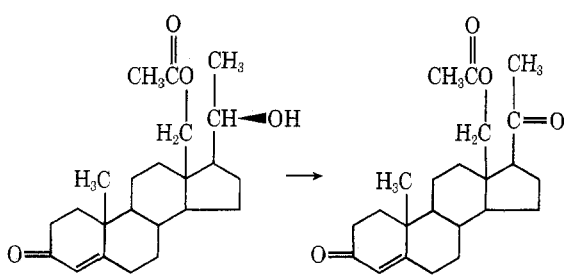
**18** **19**

Reduction of **17** with sodium bis(methoxyethoxy)aluminum hydride, under a variety of conditions, gave only the pregnene diol **18** after hydrolysis,[28] the chlorine being lost through hydrogenolysis during reduction.[18] The C-20 alcohol was assigned the $\beta$ configuration and this was proven by comparison with an authentic sample prepared from 3$\beta$,20$\beta$-dihydroxypregn-5-en-18-oic acid 18→20-lactone 3-acetate (**19**).[29] Cleavage of the 3$\beta$-acetate of **19** followed by Oppenauer oxidation,[30] ketalization,[27] and hydride reduction, followed by ketal hydrolysis gave this authentic sample of **18**.[31]

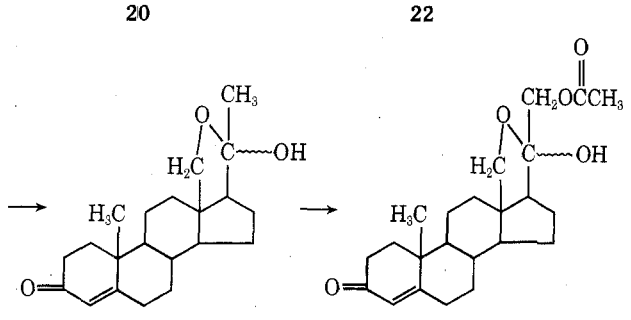
Since the 18,20-diol **18** was so conveniently accessible, it was desired to convert this compound into 18-hydroxyprogesterone (**1**), and then into 18-hydroxydeoxycorticosterone (**2**) using Kirk's method.[5] Wehrli, as part of his elegant synthesis of batrachotoxin, had shown that it was possible to selectively acetylate at the C-18 hydroxyl of an 18,20-diol and recycle the undesired 18,20-diacetate.[32] When **18** reacted with acetic anhydride in pyridine for a short time, two products were formed in a ratio of 2:3 and easily separated by low-pressure column chromatography. These were identified as the 18,20$\beta$-bisacetate **21** and 18-monoacetate **20**, the latter of which was easily identified by the downfield shift of the C-18



**21**



**20** **22**



**1** **23**

hydrogens upon acetylation.[33] Jones oxidation of **20** gave 18-acetoxyprogesterone (**22**), which was cleaved by sodium hydroxide to 18-hydroxyprogesterone (**1**). Treatment of **1** with lead tetraacetate in acetic acid, according to Kirk,[5] gave 18-hydroxydeoxycorticosterone acetate (**23**).[34]

## Experimental Section

**General.** Melting points were run on a Thomas-Hoover Unimelt capillary apparatus and are uncorrected. Ir spectra were run in potassium bromide, unless otherwise stated, on a Beckman IR-12. Ultraviolet spectra were run in methanol on a Beckman DK-2a spectrophotometer, and optical rotations were run in chloroform on a Perkin-Elmer Model 141 polarimeter. NMR spectra were recorded on a Varian A-60 or XL-100 spectrometer and were run in deuteriochloroform using tetramethylsilane as an internal standard. The NMR spectra are reported in chemical shifts ($\delta$), followed by a first-order analysis of the signal shape: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. The multiplicity is followed by the coupling constant in hertz where appropriate, and then the integrated signal intensity. Microanalyses were determined by the Searle Laboratories Microanalytical Service under the direction of Mr. E. Zielinski.

**21-Chloro-20$\beta$-hydroxypregn-4-en-3-one (5).** Deoxycorticosterone (200 g), Searle Chemicals, was dissolved in 200 ml of collidine in a 12-l. flask and then 800 ml of benzenesulfonyl chloride was added. The mixture was stirred mechanically under nitrogen for 18 h and then 4 l. of petroleum ether was added to the flask. After stirring for

2 h, the petroleum ether was siphoned off and the process was repeated three more times. During the third washing the oily residue started to crystallize. At the fourth washing, the residue was allowed to crystallize under the petroleum ether for 48 h. The crystalline material was then filtered and air dried for 0.5 h, and then dissolved in 2 l. of methylene chloride and washed with distilled water until the washings gave a negative silver nitrate test. The methylene chloride solution was dried with sodium sulfate, filtered, and evaporated to give crude 21-chloroprogesterone. Lithium aluminum hydride (30 g) was dissolved in 5 l. of dry tetrahydrofuran in a 12-l. flask. The crude 21-chloroprogesterone was slurried with 3 l. of dry tetrahydrofuran and added to the $LiAlH_4$ solution during a 15-min period. The internal temperature of the reaction solution rose from 25 °C to 45 °C during this period. After a further 15 min, 450 ml of saturated Rochelle salt solution was added and the mixture stirred overnight. The organic layer was separated and divided into three portions. Each portion was washed with 1 l. of saturated Rochelle salt solution, separated, combined with the other organics, and evaporated. The crude residue, consisting mainly of 21-chloro-3$\beta$,20$\beta$-dihydroxypregn-4-ene, was dissolved in 3 l. of benzene and 5 l. of methylene chloride, dried with sodium sulfate, and reacted for 18 h with 100 g of freshly recrystallized dichlorodicyanobenzoquinone. After this time, TLC indicated the presence of a small amount of starting material, and a further 15 g of DDQ was added and the reaction continued for a further 2 h. The reaction mixture was filtered from precipitated hydroquinone and the filter cake washed with 2 l. of methylene chloride. The solvents were removed and 70 g of residue were chromatographed on two 1700-g silica columns, eluting with benzene–ethyl acetate mixtures and taking 1-l. fractions. Elution with ethyl acetate–benzene (2:98) gave 8.06 g of progesterone, identified by comparison with an authentic sample. This was followed by 2.38 g of a mixture and then 27.13 g of the chlorohydrin **5**: mp 159–161 °C (ether–petroleum ether); $\nu$ 3480, 1670, 1615 $cm^{-1}$; uv 242 nm ($\epsilon$ 14 000); NMR $\delta$ 5.75 (s, 1 H, C-4H), 3.33–3.83 (m, 3 H, C-20,21 H), 1.22 (s, 3 H, C-19), 0.85 (s, 3 H, C-18).

Anal. Calcd for $C_{21}H_{31}ClO_2$: C, 72.29; H, 8.38; Cl, 10.16. Found: C, 72.23; H, 8.60; Cl, 10.30.

Elution with ethyl acetate–benzene (1:9) gave 14.53 g of 20$\beta$-hydroxypregn-4-en-3-one, identical with an authentic sample.

**21-Chloro-20$\beta$-hydroxy-18-nitrosopregn-4-en-3-one (8).** Into a solution of 5.0 g (14.3 mmol) of chlorohydrin **5** in 50 ml of pyridine, immersed in an ice bath, a stream of nitrosyl chloride gas was passed until red fumes filled the flask. After stirring for an additional 5 min, the suspension was poured into 400 ml of cold distilled water and stirred until solidification was complete. The crude 20$\beta$-nitrite ester was filtered and, because of its instability, immediately dissolved in 300 ml of benzene and filtered through a sodium sulfate cone. The sodium sulfate cone was rinsed with a further 100 ml of cold benzene. The nitrite solution was irradiated, under nitrogen, with a 450-W Hanovia medium pressure arc (Pyrex filter) for 1 h. The precipitate of the nitroso compound was filtered (3.80 g). Concentration of the irradiation solution gave a further 0.20 g (total 8.73 mmol, 61%) of 21-chloro-20$\beta$-hydroxy-18-nitrosopregn-4-en-3-one (**8**) as the benzene solvate: mp 120–123 °C, resolidifies and melts at 161–163 °C (methylene chloride–benzene); uv 240 nm ($\epsilon$ 16 500), 300 (3000); $\nu$ 3460, 1675, 1625 $cm^{-1}$; NMR $\delta$ 5.75 (s, 1 H, C-4), 5.39 (d, $J$ = 15 Hz, 1 H, C-18 H), 3.70 (d, $J$ = 15 Hz, 1 H, C-18 H), 3.67–4.25 (m, 3 H), 1.22 (s, 3 H, C-19).

Anal. Calcd for $C_{21}H_{30}ClNO_3 \cdot C_6H_6$: C, 70.80; H, 7.92; Cl, 7.74; N, 3.06. Found: C, 70.44; H, 8.01; Cl, 7.95; N, 3.30.

**21-Chloro-18-nitrosoprogesterone (9).** The chlorohydrin **8** (698 mg, 1.52 mmol) was dissolved in 125 ml of analytical reagent acetone and stirred magnetically at room temperature. Then 5 ml of Jones reagent (20 equiv) was added and the mixture stirred for 0.5 h. The excess reagent was destroyed with isopropyl alcohol. The bulk of the acetone was removed, distilled water added, and the remainder of the acetone evaporated. The resultant white crystals were filtered and dried in vacuo over refluxing toluene to yield 524 mg (1.39 mmol, 92%) of 21-chloro-18-nitrosoprogesterone (**9**): mp 146 °C foams, turned yellow brown to red and decomposed over 200 °C; uv 240 nm ($\epsilon$ 16 000), 298 (4000); $\nu$ 1730, 1680, 1625 $cm^{-1}$; NMR $\delta$ 5.73 (s, 1 H, C-4), 4.70 (d, $J$ = 14 Hz, 1 H, C-18 H), 4.23 (s, 2 H, C-21), 3.77 (d, $J$ = 14 Hz, 1 H, C-18 H), 1.25 (s, 3 H, C-19).

Anal. Calcd for $C_{21}H_{28}O_3ClN \cdot 0.5\ H_2O$: C, 65.19; H, 7.55; Cl, 9.16; N, 3.62. Found: C, 64.98; H, 7.39; Cl, 9.43; N, 3.71.

**21-Chloro-20$\beta$-hydroxy-18-oximinopregn-4-en-3-one (10).** The nitrosochlorohydrin **8** (250 mg, 0.55 mmol) was suspended in 30 ml of isopropyl alcohol and refluxed for 0.5 h. As the solvent, warmed, the compound went into solution. The solution was then diluted with distilled water and the majority of the alcohol evaporated to yield a white precipitate of 21-chloro-20$\beta$-hydroxy-18-oximinopregn-4-en-3-one (**10**, 200 mg, 0.55 mmol, 100%): mp 165–167 °C, foams and turns brown; uv 240 nm ($\epsilon$ 25 500); ir 3320, 1665, 1625 $cm^{-1}$; NMR $\delta$ 7.46 (s, 1 H, oxime NH), 5.75 (d, $J \cong$ 1.5 Hz, 1 H, C-4 H), 3.5–3.92 (m, 3 H), 1.13 (s, 3 H, C-19).

Anal. Calcd for $C_{21}H_{30}O_3ClN$: C, 66.39; H, 7.96; Cl, 9.33; N, 3.69. Found: C, 66.51; H, 7.96; Cl, 9.13; N, 3.49.

**18-Acetoxyimino-21-chloro-20$\beta$-hydroxypregn-4-en-3-one (11).** A suspension of 21-chloro-20$\beta$-hydroxy-18-oximinopregn-4-en-3-one (**10**, 733 mg, 1.74 mmol) in 5 ml of methylene chloride was reacted with 3 ml of acetic anhydride until all the oxime had dissolved (approximately 5 min). TLC was not useful since the oxime and the oxime acetate had identical mobilities. The methylene chloride was evaporated in vacuo and the acetic anhydride solution diluted with ether and scratched whereupon 501 mg (1.19 mmol, 69%) of 18-acetoxyimino-21-chloro-20$\beta$-hydroxypregn-4-en-3-one (**11**) crystallized: mp 138–139 °C; uv 240 nm ($\epsilon$ 16 000); $\nu$ 3430, 1775 (oxime acetate), 1670 (sh), 1650, 1615 $cm^{-1}$; NMR $\delta$ 7.63 (s, 1 H, oxime NH), 5.70 (d, $J \cong$ 0.5 Hz, 1 H, C-4 H), 3.60 (m, 3 H, C-20, 21 H), 2.15 (s, 3 H, oxime acetate methyl), 1.15 (s, 3 H, C19).

Anal. Calcd for $C_{23}H_{32}O_4ClN$: C, 65.47; H, 7.64; Cl, 8.40; N, 3.32. Found: C, 65.77; H, 7.65; Cl, 8.42; N, 3.34.

**18-Acetoxyimino-21-chloroprogesterone (12).** A solution of 501 mg of 18-acetoxyimino-21-chloro-20$\beta$-hydroxypregn-4-en-3-one (1.19 mmol) in 100 ml of analytical reagent acetone was oxidized with 2 ml of Jones reagent (8 equiv) for 10 min. The excess reagent was destroyed with isopropyl alcohol and the reaction mixture diluted with distilled water. The majority of the acetone was removed on a rotary evaporator and the white, crystalline precipitate of 18-acetoxyimino-21-chloroprogesterone (**12**, 389 mg, 0.93 mmol, 78%) collected: mp 108–111 °C; uv 240 nm ($\epsilon$ 16 000); $\nu$ 1770 (oxime acetate), 1740 (chloro ketone), 1675, 1625 $cm^{-1}$ (enone); NMR $\delta$ 7.70 (s, 1 H, oxime NH), 5.75 (s, 1 H, C-4 H), 4.42 (s, 2 H, C-21 H), 2.12 (s, 3 H, oxime acetate methyl), 1.17 (s, 3 H, C-19).

Anal. Calcd for $C_{23}H_{30}O_4ClN$: C, 65.78; H, 7.20; Cl, 8.44; N, 3.34. Found: C, 65.95; H, 7.46; Cl, 8.36; N, 3.30.

**18-Acetoxyiminodeoxycorticosterone Acetate (13).** A solution of 858 mg (2.04 mmol) of 18-acetoxyimino-21-chloroprogesterone (**12**) in 100 ml of analytical reagent acetone, 5 g of potassium acetate, and 5 g of sodium iodide was stirred vigorously and brought to reflux. After 15 min, the mixture was cooled and diluted with water, and the acetone removed to give a gum. The gum was extracted into methylene chloride (250 ml). The organic solution was dried with sodium sulfate and evaporated. The residue was taken up in acetone and distilled water added until the solution had a milklike color. 18-Acetoxyiminodeoxycorticosterone acetate (**13**, 583 mg, 1.32 mmol, 65%) very slowly crystallized over an 18-h period: mp 115–118 °C; uv 240 nm ($\epsilon$ 17 000); $\nu$ 1775 (oxime acetate), 1755 ($\alpha$-acetoxy carbonyl), 1720 (C-20 ketone), 1670, 1620 $cm^{-1}$ (C-4 enone); NMR $\delta$ 7.67 (s, 1 H, oxime NH), 5.77 (s, 1 H, C-4 H), 4.73 (s, 2 H, C-21 H), 2.15 (s, 3 H, oxime acetate methyl), 2.13 (s, 3 H, C-21 acetate methyl or reversed with oxime acetate methyl), 1.18 (s, 3 H, C-19).

Anal. Calcd for $C_{25}H_{33}O_6N$: C, 67.70; H, 7.50; N, 3.16. Found: C, 67.79; H, 7.40; N, 3.21.

**18-Nitrilodeoxycorticosterone Acetate (14).** 21-Chloro-20$\beta$-hydroxy-18-nitrosopregn-4-en-3-one (**8**, 5.0 g, 10.92 mmol) was converted into the oxime **10**, acetylated to the oxime acetate (**11**), oxidized to the chloro ketone (**12**), and the chlorine replaced by an acetoxy group (**13**). Without purification of any of the intermediates, 18-acetoxyiminodeoxycorticosterone acetate (**13**) was refluxed in 50 ml of pyridine for 2 h when TLC indicated conversion into the nitrile. The pyridine was removed and the residue chromatographed on 500 g of silica. Elution with ethyl acetate–benzene (1:9) gave 1.36 g from which 1.05 g of 18-nitrilodeoxycorticosterone acetate (**14**, 2.74 mmol, 25% based on **8**) could be isolated by crystallization from ether: mp 151–153 °C; $\nu$ 2240 (C≡N), 1755 (acetoxy carbonyl), 1740 (C-20 ketone), 1670, 1620 $cm^{-1}$ (C-3 enone); NMR $\delta$ 5.78 (s, 1 H, C-4 H), 4.72 (s, 2 H, C-21 H), 2.15 (s, 3 H, acetoxy methyl H), 1.25 (s, 3 H, C-19).

Anal. Calcd for $C_{23}H_{29}O_4N$: C, 72.03; H, 7.62; N, 3.65. Found: C, 71.88; H, 7.64; N, 3.39.

**18-Nitrilodeoxycorticosterone (15).** A solution of 538 mg (1.40 mmol) of 18-nitrilodeoxycorticosterone acetate (**14**) in 250 ml of methanol containing 250 mg of *p*-toluenesulfonic acid monohydrate was refluxed. After 22 h, 150 ml of distilled water was added and the majority of the methanol removed on a rotary evaporator. The milky solution was extracted with methylene chloride (5 × 150 ml) and the combined extracts dried with sodium sulfate. The methylene chloride was removed and the residue crystallized from ether–petroleum ether to yield 339 mg (0.97 mmol, 69%) of 18-nitrilodeoxycorticosterone (**15**):

mp 110–112 °C; uv 238 nm (ε 15 000); ν 3400, 2240 (C≡N), 1730 (C-20 ketone), 1670, 1660, 1620 cm$^{-1}$ (enone); NMR δ 5.75 (s, 1 H, C-4 H), 4.30 (m, 2 H, C-21 H), 1.25 (s, 3 H, C-19).

Anal. Calcd for $C_{21}H_{27}O_3N \cdot 0.5\ H_2O$: C, 71.97; H, 8.05; N, 4.00. Found: C, 71.62, 71.66; H, 7.91, 7.90; N, 3.74, 4.09.

**21-Chloro-20β-hydroxy-3-oxopregn-4-en-18-oic Acid 18→20-Lactone (16).** A suspension of 5 g of calcium carbonate and 15 g of dry lead tetraacetate in 500 ml of cyclohexane was brought to reflux and 25 ml of solvent removed (Dean-Stark trap). To this refluxing suspension was added 1.8 g of iodine and 5.0 g (14.3 mmol) of chlorohydrin **5** and the mixture irradiated in a Rayonet preparative photoreactor with eight 3500-Å lamps until the iodine color disappeared (1.75 h). After cooling, the mixture was filtered and the filter cake washed with methylene chloride. The combined organics were washed with dilute sodium sulfate solution, separated, dried with sodium sulfate, and evaporated. The residue was taken up in acetone and oxidized, at 0 °C, with excess Jones reagent for 15 min. The excess oxidant was quenched with isopropyl alcohol, distilled water was added, and the majority of the acetone was removed on a rotary evaporator to give a gum. The gum was extracted in methylene chloride and the organic solution dried with sodium sulfate and evaporated. The residue was dissolved in 500 ml of acetone, 15 g of potassium iodide and 15 g of potassium acetate were added, and the mixture was refluxed for 0.5 h. Distilled water was added and the acetone evaporated. The residue was extracted into methylene chloride, the organics were dried with sodium sulfate and evaporated, and the residue was chromatographed on 500 g of silica. Elution with ethyl acetate–benzene (1:99) gave 1.93 g from which 1.31 g (3.62 mmol, 25%) of the 18→20 lactone **16** could be crystallized using ethyl acetate–petroleum ether: mp 187–190 °C; ν 1765, 1670, 1615 cm$^{-1}$; uv 240 nm (ε 16 500); NMR δ 5.80 (s, 1 H, C-4 H), 1.28 (s, 3 H, C-19).

Anal. Calcd for $C_{21}H_{27}O_3Cl$: C, 69.50; H, 7.50; Cl, 9.77. Found: C, 69.64; H, 7.71; Cl, 9.79.

There was no TLC evidence for the presence of any 18-hydroxydeoxycorticosterone acetate.

**The 18→20 Lactone from Oxidation of the Oxime 10.** A solution of 750 mg of oxime **10** (1.98 mmol) in 250 ml of analytical reagent acetone was oxidized with 2 ml of Jones reagent. After 5 min, the excess reagent was destroyed with isopropyl alcohol, the reaction solution diluted with distilled water, and the acetone removed in vacuo to yield 439 mg (1.21 mmol, 61%) of the 18→20 lactone **16**.

**Reduction of the 21-Chloro-18→20-lactone 16.** A suspension of lactone **16** (2.60 g, 7.16 mmol) in 350 ml of ethylene glycol, containing 0.216 g of *p*-toluenesulfonic acid monohydrate, was distilled at 70–80 °C and ~1 mm. After 250 ml had been distilled, the distillation was stopped and the pot residue cooled to room temperature. After the addition of 1 ml of pyridine, the suspension was diluted with 300 ml of distilled water and filtered. The precipitate was washed with a further 500 ml of distilled water and dried to yield 2.77 g (6.81 mmol, 95%) of the ethylene ketal **17**. This was not characterized, except to note the absence of enone absorptions in the ir and uv.

A solution of 2.0 g (4.91 mmol) of the above ketal in 150 ml of benzene was dried by azeotropic distillation of 10 ml of solvent (Dean-Stark trap). The solution was blanketed with nitrogen and when the internal temperature reached 50 °C, 5 ml of sodium bis(methoxyethoxy)aluminum hydride (70% in toluene) was added. After 1 h reflux, the solution was cooled and carefully quenched with 50 ml of saturated Rochelle salt. Since there was an appreciable amount of solid at the organic–aqueous interface, 200 ml of chloroform was added and the solid dissolved. The aqueous was separated and discarded and the organics dried with sodium sulfate and evaporated. The solid so obtained was partially dissolved in 50 ml of tetrahydrofuran and treated with 37.5 ml of 2.8 M perchloric acid. After 5 min, 200 ml of water was added and the mixture was extracted with chloroform (3 × 100 ml). The combined organics were washed with 0.5 M sodium bicarbonate and then water. After drying with sodium sulfate, the solvents were removed and the oil crystallized nicely from ether to give 918 mg (2.74 mmol, 56%) of 18,20β-dihydroxypregn-4-en-3-one (**18**): mp 195.5–205 °C; ν 3500, 3470, 1675, 1625 cm$^{-1}$; uv 240 nm (ε 14 500); NMR δ 5.73 (s, 1 H, C-4 H), 3.92 (m, 1 H, C-20), 3.78 (d, $J$ = 10.5 Hz, 1 H, C-18), 3.50 (d, $J$ = 10.5 Hz, 1 H, C-18), 1.19 (s, 3 H, C-19), 1.17 (d, $J$ , 5.5 Hz, 3 H, C-21).

Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.58; H, 9.63.

**18,20β-Dihydroxypregn-4-en-3-one (18).** A solution of 1.85 g of 3β-acetoxy-20β-hydroxypregn-5-en-18-oic acid 18→20-lactone in 50 ml of methanol was saponified with 5 g of sodium hydroxide. After 0.5 h, the solution was diluted with 200 ml of distilled water, acidified with 10 ml of concentrated hydrochloric acid, and the majority of the methanol removed on a rotary evaporator. The crude 3β,20β-dihydroxypregn-5-en-18-oic acid 18→20-lactone was filtered, dried, and oxidized using the Oppenauer reaction to yield 1.3 g of 20β-hydroxy-3-oxopregn-4-en-18-oic acid 18-20-lactone, mp 205–208 °C (lit. 206–208 °C).[31] The 1.3 of lactone was converted into the 3-ethylene ketal in a manner exactly analogous to the 21-chlorolactone **16** to give 1.3 g of ketal. The ketal was not characterized but was reduced directly using sodium bis(methoxyethoxy)aluminum hydride analogously to **17**. After cleavage of the ketal with perchloric acid in tetrahydrofuran and crystallization from ether, 670 mg of authentic 18,20β-dihydroxypregn-4-en-3-one, mp 200–205 °C (lit. 206–209 °C),[31] was isolated. This sample was identical in every way with the compound isolated from the reduction of 21-chlorolactone **16**.

**Selective Acetylation of 18,20β-Dihydroxypregn-4-en-3-one (18).** The diol **18** (615 mg, 1.85 mmol) was dissolved in 6 ml of pyridine and 5 ml of acetic anhydride. The reaction mixture was held at 0 °C for 4 h when the reaction mixture was quenched with methanol. The reaction mixture was poured into water and extracted with methylene chloride. The methylene chloride solution was washed with water and extracted with dilute hydrochloric acid. After drying with sodium sulfate, the solvent was removed and the residue subjected to low-pressure liquid chromatography on a 9-mm Woelm silica column. Elution with ethyl acetate–benzene (1:4) gave 190 mg (0.46 mmol, 25%) of 18,20β-dihydroxypregn-4-en-3-one diacetate (**21**): mp 112 °C soften, melts 115.5–129 °C; ν 1740, 1680, 1620 cm$^{-1}$; uv 240 nm (ε 17 000); NMR δ 5.73 (s, 1 H, C-4), 4.80 (broad s, 1 H, C-20), 4.28 (d, $J$ = 12 Hz, 1 H, C-18), 3.82 (d, $J$ = 12 Hz, 1 H, C-18), 2.02 (s, 6 H, acetate methyls), 1.17 (d, $J$ = 6 Hz, 3 H, C-21), 1.18 (s, 3 H, C-19).

Anal. Calcd for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71. Found: C, 71.96; H, 8.58.

Elution with ethyl acetate–benzene (1:3) gave 256 mg (0.69 mmol, 37%) of 18,20β-dihydroxypregn-4-en-3-one 18-acetate (**20**): mp 135–140.5 °C; ν 3500, 1745, 1675, 1620 cm$^{-1}$; uv 240 nm (ε 16 500); NMR δ 5.75 (s, 1 H, C-4), 4.42 (d, $J$ = 12 Hz, 1 H, C-18), 3.85 (d, $J$ = 12 Hz, 1 H, C-18), 3.67–4.00 (m, 1 H, C-20), 1.30 (s, 3 H, 18-acetate methyl), 1.20 (s, 3 H, C-19), 1.15 (d, $J$ = 6 Hz, 3 H, C-21).

Anal. Calcd for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.54; H, 8.96.

Elution with ethyl acetate–benzene (3:7) returned 143 mg (0.43 mmol, 23%) of starting diol **18**.

**18-Acetoxyprogesterone (22).** A solution of 158 mg of 18,20β-dihydroxypregn-4-en-3-one 18-acetate (**20**, 0.42 mmol) in 50 ml of analytical reagent acetone at 0 °C was oxidized with 0.15 ml of Jones reagent for 5 min. The excess reagent was quenched with isopropyl alcohol and distilled water added. After the majority of the acetone was removed on a rotary evaporator, the 18-acetoxyprogesterone was extracted into 50 ml of methylene chloride. The organic solution was dried with sodium sulfate and evaporated. Crystallization from petroleum ether using a little ether slowly gave 142 mg (0.38 mmol, 91%) of 18-acetoxyprogesterone: mp 135–137 °C (lit. 136.5–137.5 °C);[3] ν 1745 (acetate carbonyl), 1710 (C-20 carbonyl), 1675, 1620 cm$^{-1}$ (enone); NMR δ 5.75 (s, 1 H, C-4), 4.22 (d, $J$ = 12 Hz, 1 H, C-18), 3.83 (d, $J$ = 12 Hz, 1 H, C-18), 2.20 (s, 3 H, C-18 acetate methyl), 1.98 (s, 3 H, C-21), 1.19 (s, 3 H, C-19).

**18-Hydroxyprogesterone.** To a solution of 100 mg (0.27 mmol) of 18-acetoxyprogesterone (**22**) in 12 ml of methanol was added 5 ml of 2 N sodium hydroxide and the mixture refluxed, under nitrogen, for 1.5 h. The reaction mixture was poured into water and extracted with methylene chloride. After drying with sodium sulfate, the methylene chloride was removed on a rotary evaporator and the residue crystallized from ether to yield 77 mg (0.23 mmol, 86%) of 18-hydroxyprogesterone (**1**), mp 175–178 °C (lit. 173–182 °C),[2] identical with an authentic sample from R. Pappo.

**18-Hydroxydeoxycorticosterone 21-Acetate (23).** To a stirred solution of 121.4 mg of 18-hydroxyprogesterone in 4 ml of acetic acid was added 0.5 g of dry lead tetraacetate. After 4 h, 1 ml of glycerine was added to destroy the excess lead tetraacetate and after a further 1 h, the reaction mixture was poured into water. From this milky solution, 18-hydroxydeoxycorticosterone acetate (**23**, 71 mg) slowly crystallized. This material was identical with an authentic sample from R. Pappo.

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# The He I Photoelectron Spectra of *N*-Methylisoindole and *N*-Methylindole


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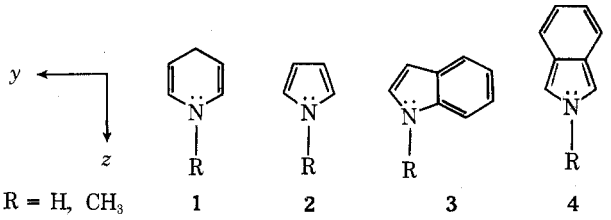
The He I photoelectron spectra of *N*-methylisoindole and *N*-methylindole are reported. The first three bands of the isoindole are assigned to $^2A_2$ (7.22 eV), $^2B_1$ (8.48 eV) and $^2A_1$ (9.51 eV) ionic states of the $C_{2v}$ molecular geometry. Predictions of INDO, Hückel, and structure representation models for the indoles pyrrole and 1,4-dihydropyridine are compared.


The high reactivity of isoindoles has excited many previous experimental[1] and theoretical investigations.[1,2] We presently wish to report the results of our determination of the He I photoelectron spectra of *N*-methylindole (**3**) and *N*-methylisoindole (**4**) and a comparison of the predictions of INDO–SCF,[3] Hückel,[4] and structure representation[5] (SR) models for the ordering of the ionic states of these molecules.




R = H, $CH_3$ 1 2 3 4

*N*-Methylindole was prepared from *N*-methylindole-2-carboxylic acid by decarboxylation. *N*-Methylisoindole was prepared from *N,N*-dimethylisoindolinium bromide by treatment with phenyllithium.[6] It was isolated by an extraction under nitrogen and purified by sublimation under high vacuum (<0.05 Torr). Photoelectron spectra of this compound were recorded immediately after breaking open the sealed sublimation tube containing the purified material so that contact time of the sample with air was less than 2 min. A small amount of volatile impurity was evident in the initial spectra but disappeared after a short period in the vacuum chamber of the spectrometer. The spectrum of **4**, shown in Figure 1, is typical of those reproducibly obtained after the initial 30 min of pumping.[6a] The observed and calculated vertical ionization potentials for the series **1–4**, using several methods, are summarized in Table I.

The INDO–SCF method gives the first ionic configuration of **4** ($C_{2v}$) as $^2A_2$ and the second as $^2B_1$. The differences[11] in the energies of these ionic configurations and that for the ground state are 8.31 and 9.80 eV, respectively. The former